REMARKS

Claims 40, 45 and 48-49 are now pending.

Applicants note that there have been extensive and unnecessary prosecution of this application caused by the frequent change of Examiners. Indeed, the claims had largely been considered allowable by the previous Examiner. Thus, Applicants request the present Examiner to consider the arguments presented herein favorably to avoid further delay in allowance of this application.

On page 2 of the Office Action, the Examiner rejects Claim 40 under 35 U.S.C. § 102(b) as being anticipated by Ogreid et al.

Specifically, the Examiner contends that Ogreid et al teaches Rp-piperidino-cAMPs in a solution.

In view of the amendment to Claim 40 to delete Rp-piperidino-cAMPs, this rejection is deemed to be moot.

On pages 3-5 of the Office Action, the Examiner rejects Claim 45, 48 and 49 under 35 U.S.C. § 103 as being anticipated by Gjertsen et al in view of Hoffmann et al and Jastorff et al.

Specifically, it is the Examiner's position that Gjertsen et al teaches a method of inhibiting cAMP with a cAMP antagonist, i.e., Rp-8-Br-cAMPS, Rp-8-Cl-cAMPS or Rp-8-4-chlorophenyl-thio-cAMPs. The Examiner notes that Gjertsen et al does not teach administering a cAMP antagonist to a subject in need thereof, as claimed in the present application. However, it is the Examiner's position that such would have been obvious to one skilled in the art so as to restore T-cell function, since Hoffmann et al teaches that

reducing cAMP levels restores T-cell function, which the Examiner contends is crucial because HIV-positive individuals without AIDS have significant increases in intracellular cAMP levels, and Gjertsen et al teaches that inhibition of cAMP results in enhanced DNA replication, which would result in an increased T-population. Further, the Examiner contends that it would have been obvious to use Rp-8-Br-CAMPS, Rp-8-Cl-cAMPS or Rp-8-4-chlorophenyl-thio-cAMPs, because each were known to be cAMP antagonists, and Jastorff et al teaches administration of Rp-Cl-cAMP *in vivo* and that such is more resistant to hydrolysis, rendering such a better candidate as a chemotherapeutic agent.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Hoffmann et al contains experiments which demonstrate that cAMP is found at high levels in lymphoid cells from HIV seropositive subjects. The authors hypothesize that high intracellular cAMP concentrations play a role in the diminished function of non-infected T cells in HIV seropositive subjects. This was tested by *in vitro* studies in which PBMC from HIV seropositive subjects were treated with an inhibitor of adenylate cyclase, which is responsible for the generation of cAMP (see page 661 of Hoffmann et al, right hand column, second paragraph). The direct addition of the inhibitor to microcultures of PBMC from HIV seropositive subjects *in vitro* was shown to restore proliferation to a recall antigen under the conditions used in these *in vitro* experiments. In addition, cytotoxic T cells from HIV seropositive subjects regained their

normal ability to lyse an allogenic tumor cell line in the presence of ddAdo in several *in vitro* experiments. The authors then suggest that restoration of normal T cell functions should be of great benefit in the treatment of HIV infection and that reduction of cAMP and improved function *in vivo* may be possible by treatment with agents such as those described here in two *in vitro* experiments (i.e., inhibitors of adenylate cyclase). Thus, Hoffmann et al only teaches that inhibiting cAMP generation in an *in vitro* model increases T cell responses, when measured in the context of a PBMC population.

A person having ordinary skill in the art to which the subject matter of the claims pertains would have at that time learnt from Hoffmann et al that cAMP levels are elevated in PBMC in HIV patients and that reducing cAMP levels in PMBC has an effect on T cell proliferation *in vitro*, and therefore reducing cAMP levels might be one option for treating HIV, by inhibiting its generation by the enzyme adenylate cyclase.

However, it is important to bear in mind that cAMP is a signalling molecule that has many functions in cells. It is responsible for controlling many pathways and many biological processes in all cell types. This is referred to, for example, on page 2 of the present application. cAMP acts as a signalling molecule in pathways that are regulated by numerous hormones, neurotransmitters, cytokines, inflammatory mediators and other extracellular substances. It is involved in the regulation of heart rate and contraction force, arginine-vasopressin(AVP)-induced redistribution of acquaporin-2 (AQP2) from intracellular vesicles to the plasma membrane of

renal collection duct principal cells (AQP2 shuttle) leading to water reabsorption in the kidney, renin secretion from renal juxtaglomerular cells, insulin secretion from pancreatic beta-cells, acid secretion in the stomach, bronchoconstriction in the airways, fat metabolism in adipocytes, control of brain functions, steroid production in adrenal glands and gonads, cell migration and, sperm motility and a number of other processes including gene regulation and cell cycle regulation and differentiation.

Dysregulation of cAMP-dependent signalling is involved in the development and progression of a number of diseases including hypertension and heart failure, diabetes mellitus, diabetes insipidus, states of water retention, obesity, neurological disorders including schizophrenia, chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD), and affects anti-tumor immune responses.

cAMP performs all of these functions by interacting with various other signalling molecules, for example, it can act via a whole class of cyclic nucleotide gated ion channels, through a pathway involving guanine exchange factors of the Epac class that regulates small G proteins of the Rap1 and Rap2 type, and various pathways in which different PKA isozyme forms play a role. As noted in the specification, PKA exists in many different isozyme forms.

It is thus clear that the effect demonstrated in Hoffmann et al could be attributed to <u>any</u> one of these pathways, or indeed it could be a <u>non-specific</u> effect. Hoffmann et al

merely states that the cAMP may be involved in T cell proliferation. In view of its diverse effects, inhibiting cAMP formation is likely to affect a large number of different pathways in a cell. Hoffmann et al do not indicate how to apply this teaching to the treatment of diseases, other than by administering inhibitors of cAMP formation. There is therefore no teaching in Hoffmann et al whatsoever to use specific inhibitors of the PKA Iα pathway as claimed in the present invention. Clearly, administering such broad-spectrum inhibitors as AC inhibitors would be undesirable owing to the large member of undesirable side-effects which are likely to result from inhibiting all cAMP signalling pathways. Hoffmann et al does not, of course, illustrate whether affecting all cAMP pathways of all cells would be beneficial *in vivo* or whether major side-effects, due to the lack of specificity might be observed. Several of the pathways that would be affected by a general cAMP inhibitor are likely to downregulate T cell proliferation and thus comprise the positive effects that might be achieved. Indeed, Hoffmann et al fails to provide any *in vivo* data, in particular of whether T cell proliferation might be affected *in vivo*.

In direct contrast to the teaching in Hoffmann et al, Claim 45 refers a method using inhibitors that are specific for the inhibition of PKA type Iα, which is one particular PKA type out of 18 possible PKA types. Nowhere in Hoffmann at al does it suggest that the particular pathway that is mediated by PKA type Iα should be inhibited in order to increase T cell proliferation in a subject in need thereof. The invention is

directly related to Applicants' observation that specific inhibition of this particular PKA type is beneficial to increase T cell proliferation in a subject in need thereof. This has been demonstrated *in vitro* in respect of the effect on T cells isolated from HIV and CVI patients in the Examples of the present application, and *in vivo* in data provided in the Declaration filed on June 19, 2002 (a 3 fold increase in CD3 induced proliferation of MAIDS T cells was observed after treatment with Rp-8-Br-cAMPS).

The identification of this specific pathway in the present invention, as the pathway of relevance in T cell dysfunction *in vivo* allows the targeting of just this specific pathway and avoids the plethora of undesirable effects that would otherwise follow using non-specific targeting of all cAMP pathways. As mentioned above, the application has been validated *in vivo*.

Although certain PKA type Iα inhibitors were known at the date of the invention, there is nothing in the cited documents that would indicate that they could be used to treat a subject in need of enhanced T cell proliferation. In the present invention, specific cAMP antagonists have been selected which are specific for PKA type Iα.

Jastorff et al suggests that cAMP antagonists might <u>not</u> be useful for improving proliferation. Firstly, it is indicated that the effects of cAMP on cell proliferation are contradictory (see pages 2 and 3). In particular on page 3, the contradictory results obtained on proliferation of lymphocytes are discussed. This is a clear teaching <u>against</u> using such compounds in the context of enhancing proliferation of T cells.

In the growth inhibition studies described in Jastorff et al, cAMP analogues are used and advocated. These analogues encompass both agonists (the Sp diastercomer) and antagonists (Rp diastereomer). Both of these compounds inhibited growth (see Figure 10 which shows the effects of such compounds on HL-60 leukemia cells). The Examiner is requested to note that cAMP antagonists are therefore taught in Jastorff et al to inhibit growth, and would therefore not be contemplated for use in a method which is required to cause a positive effect on cell proliferation. In contrast, the present application contains *in vitro* data on T cells and *in vivo* data has been presented in the Declarations of record which demonstrate that the antagonists as defined in Claim 45 have the desired effects on T cell proliferation in the appropriate context, contrary to the expectation in the art.

The Examiner's argument that, Jastorff et al provides the skilled person with a reasonable expectation of success in view of the administration in Jastorff et al of cAMP antagonists *in vivo* is thus inappropriate. Jastorff et al fails to show that enhanced T cell proliferation would be achieved. As such, it cannot illustrate a reasonable expectation of success.

Furthermore, although this was not appreciated at the time, it is now believed that some of the contradictory effects of these compounds described in the prior art can, in fact, be attributed to the use of impure compounds which were a mixture of Rp and Sp diastereomers. At the time that the prior art experiments were carried out (Jastorff et al has a priority date of May 1, 1992), it was difficult to control the

stereochemistry, and this resulted in contamination of the preparations with the undesired diastereomer. The experiments described in the present application and Declarations used purified preparations.

In regard to Gjertsen et al, this reference simply examines the effect of various compounds on PKA. DNA replication was one of the parameters that was measured, although it should be noted that no lymphocytes mere used its this system, only a promyelocytic leukaemia cell line (IPC 81), fibroblasts transfected with PKA type I or II (which is an artificial system) and hepatocytes were used. Gjertsen et al does not perform any experimental work based on T cells. Absent any identification of the relevance of targeting PKA type I to achieve T cell proliferation, Gjertsen et al does not teach the usefulness of the recited compounds for achieving T cell proliferation. Indeed, if the skilled person had assessed proliferation of T cells with the recited compounds, no proliferation would have been observed.

It is clear from the Examples of the present application that when PKA antagonists that are specific to PKA type Iα (such as those used in Example 1 of the present application, see page 17 of the application as published) are administered to T cells, whilst improved proliferation is seen in cells that are from HIV infected patients, there is no effect on proliferation of normal T cells (see Figure 3b). This is now known to be due to the fact that in normal cells there is no enhanced cAMP concentration which causes proliferation to be inhibited via PKA type Iα.

As these inhibitors have no effect on normal T cells, even if the skilled person had chosen to assess the effect of the compounds on proliferation of T cells, the results would have led the skilled person to believe that the compounds were ineffective at enhancing proliferation. Thus, it would not be obvious to the skilled person at the time the invention was made to use them to enhance T cell proliferation in a subject in need thereof.

In summary, the prior art fails to demonstrate that cAMP is necessarily implicated in the level of T cell proliferation. Significantly, the role of PKA type I as the relevant cAMP signal mediator for T cell proliferation is not taught. Indeed, several of the claimed compounds were taught to inhibit growth. No *in vivo* results have been provided. As such the identification of the role of cAMP in T cell proliferation, the identification of PKA type 1 as the mediator of the cAMP effect on T cell proliferation, the identification and use of selective antagonists to this signalling mediator and the *in vivo* evidence of utility represents a significant advance in the field, and as such should be viewed as inventive. To assert otherwise requires the use of hindsight to selectively interpret and combine prior art documents and to ignore conflicting teachings in the art, and as such is impermissible.

There is no motivation or suggestion that the compounds referred to in Claim 45 of the present application might be used to enhance T cell proliferation in a subject in need thereof, as claimed.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Gjersten et al, alone or when combined with the teachings in Hoffmann et al or Jastorff et al, and in any event such a combination can only be made in hindsight which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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